# Drosophila Kismet regulates histone H3 lysine 27 methylation and early elongation by RNA polymerase II.

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**Public Summary:**
Polycomb and trithorax group proteins regulate cellular pluripotency and differentiation by maintaining hereditable states of transcription. Many Polycomb and trithorax group proteins have been implicated in the covalent modification or remodeling of chromatin, but how they interact with each other and the general transcription machinery to regulate transcription is not well understood. The trithorax group protein Kismet-L (KIS-L) is a member of the CHD subfamily of chromatin-remodeling factors that plays a global role in transcription by RNA polymerase II (Pol II). Mutations in CHD7, the human counterpart of kis, are associated with CHARGE syndrome, a developmental disorder affecting multiple tissues and organs. To clarify how KIS-L activates gene expression and counteracts Polycomb group silencing, we characterized defects resulting from the loss of KIS-L function in Drosophila. These studies revealed that KIS-L acts downstream of P-TEFb recruitment to stimulate elongation by Pol II. The presence of two chromodomains in KIS-L suggested that its recruitment or function might be regulated by the methylation of histone H3 lysine 4 by the trithorax group proteins ASH1 and TRX. Although we observed significant overlap between the distributions of KIS-L, ASH1, and TRX on polytene chromosomes, KIS-L did not bind methylated histone tails in vitro, and loss of TRX or ASH1 function did not alter the association of KIS-L with chromatin. By contrast, loss of kis function led to a dramatic reduction in the levels of TRX and ASH1 associated with chromatin and was accompanied by increased histone H3 lysine 27 methylation-a modification required for Polycomb group repression. A similar increase in H3 lysine 27 methylation was observed in ash1 and trx mutant larvae. Our findings suggest that KIS-L promotes early elongation and counteracts Polycomb group repression by recruiting the ASH1 and TRX histone methyltransferases to chromatin.

**Scientific Abstract:**
Polycomb and trithorax group proteins regulate cellular pluripotency and differentiation by maintaining hereditable states of transcription. Many Polycomb and trithorax group proteins have been implicated in the covalent modification or remodeling of chromatin, but how they interact with each other and the general transcription machinery to regulate transcription is not well understood. The trithorax group protein Kismet-L (KIS-L) is a member of the CHD subfamily of chromatin-remodeling factors that plays a global role in transcription by RNA polymerase II (Pol II). Mutations in CHD7, the human counterpart of kis, are associated with CHARGE syndrome, a developmental disorder affecting multiple tissues and organs. To clarify how KIS-L activates gene expression and counteracts Polycomb group silencing, we characterized defects resulting from the loss of KIS-L function in Drosophila. These studies revealed that KIS-L acts downstream of P-TEFb recruitment to stimulate elongation by Pol II. The presence of two chromodomains in KIS-L suggested that its recruitment or function might be regulated by the methylation of histone H3 lysine 4 by the trithorax group proteins ASH1 and TRX. Although we observed significant overlap between the distributions of KIS-L, ASH1, and TRX on polytene chromosomes, KIS-L did not bind methylated histone tails in vitro, and loss of TRX or ASH1 function did not alter the association of KIS-L with chromatin. By contrast, loss of kis function led to a dramatic reduction in the levels of TRX and ASH1 associated with chromatin and was accompanied by increased histone H3 lysine 27 methylation-a modification required for Polycomb group repression. A similar increase in H3 lysine 27 methylation was observed in ash1 and trx mutant larvae. Our findings suggest that KIS-L promotes early elongation and counteracts Polycomb group repression by recruiting the ASH1 and TRX histone methyltransferases to chromatin.